

Book Review

Complementary and Alternative Approaches to Biomedicine

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This book, *Complementary and Alternative Approaches to Biomedicine*, contains the proceedings of the International Symposium on Complementary and Alternative Medicine (CAM) which was convened in Kanazawa Japan, November 8–10, 2002. There were participants mainly from Japan, the USA, China, France, England, Germany, Taiwan and India. What struck me from the opening chapter was the broad range of voices from all over the world. Like a good chamber orchestra, the varied voices of strings, woodwind and percussion were in balance, treating us to a breadth and depth one rarely finds in a book of conference proceedings.

With the world of Western medicine gradually opening its doors to new ways of approaching healing, of which many began centuries and even millennia ago in Asia, it was entirely appropriate to hold the symposium in Kanazawa, a beautiful, traditional city located on the Sea of Japan. Experts from Asia, Europe and the USA gathered together for true discussions on CAM and its role developing all over the world. These high quality, peer-reviewed chapters aim at significantly dispelling some of the criticisms of pseudoscience and myth that often surround the discipline.

National Approaches to CAM

Five chapters represent the first section on national approaches to CAM from Japan, Taiwan, Germany and Italy. The focus considers various practices in these regions. Suzuki *et al.* give an excellent account of the history of CAM in Japan and the USA. In 1990, a small research group of physicians interested in CAM was born at Kanazawa University. In 1997, this group established the Japanese Society for Complementary and Alternative Medicine (JCAM). The members of JCAM are doctors, nurses, dentists, veterinarians, acupuncturists, nutritionists, pharmacists and researchers of various fundamental sciences. Thus Japan remains a locale of intense activity.

Yamada and Chen's chapters focus on Kampo and Traditional Chinese Medicine (TCM), the medical systems of

their native countries, Japan and Taiwan, where they are known experts in these fields. Since Kampo medicines have originated from traditional Chinese medicines, they have long been used, reaping the valuable experience acquired during >2000 years. Therefore, Chinese medicines including Kampo are not considered alternative medicine for people in China, Japan and Korea. Although Kampo medicines have a long clinical experience that supports a belief in their efficacy and safety, all the authors agreed that Kampo as well as all other natural medicines must be evaluated by scientific clarification of mechanisms of action and the active ingredients. Chen *et al.* show the increased synergy between TCM and Western medicine in Taiwan. In Taiwan, the government has spearheaded the modernization of Chinese medicine since 1950. Instead of pitting the two major health protection systems, i.e. Chinese medicine and the Western system, against each other by confrontations and competitions, in recent years efforts have been directed at integrating those complementary aspects of the two systems into a comprehensive system, that may be referred to as integrative medicine. The results are increasingly recognized and accepted by Western nations.

In Europe, increased use of herbal medicinal products (HMPs) has required a thorough review of appropriate guidelines to evaluate them for safety and efficacy, i.e. therapeutic benefits. The generally accepted and well-structured quality management is formally laid down in the European Pharmacopoeia, where an increasing number of monographs for HMPs and the products thereof are documented (see Chapter by Franz). Quality of HMP defines the optimal specifications for each compound by specifying one or more analytical procedures, which, in association with the limits of acceptance, define qualitative (identification) and quantitative (limits for impurities and content of active ingredient) characteristics for the HMP. On the same note, Minelli *et al.* demonstrate how the WHO Collaborating Center for Traditional Medicine of the University of Milan faces all these aspects of Traditional Phytotherapy with a number of activities of research, educational training, and legal advice to several public institutions. The Research Centre in Bioclimatology,

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Biotechnology and Natural Medicine was founded in 1969, and it refers to the Departments of Normal Human Anatomy, Biochemistry, Microbiology, Medical Chemistry and Thermal Medicine. Since its establishment, the Center has dealt with issues concerning the QOL (quality of life), and it has developed research and training in this field, paying particular attention to natural and complementary medicines.

CAM Approaches to Specific Diseases and Biomedical Conditions

This second section on CAM approaches specific diseases and biomedical conditions, taking a global approach beginning with environmental concerns and the causes of disease. Despite significant advancements in medicine and identifying the human genome, mainstream practice has paid less attention to early diagnosis and prevention of complex diseases (e.g. gastrointestinal, cardiovascular, autoimmune) (see chapter by Vojdani and Cooper). These diseases cannot be ascribed to mutations in a single gene; rather they arise from the combined action of many genes, environmental factors and risk-conferring behaviors. Complementary medicine has an enormous challenge: to determine how environmental factors (infections and xenobiotics) interact.

According to the Joint United Nations Program of HIV/AIDS (UNAIDS) and the World Health Organization (WHO), as of the end of 2001, there were ~40 million adults and children living with human immunodeficiency virus (HIV) infection. (see chapter by Cossarizza and his students). The large majority (almost three-quarters) live in Sub-Saharan Africa where the prevalence rate of the infection among adults is 8.4%; >55% of infected individuals are women, with growing numbers all over the world. In 1995, the introduction of highly active antiretroviral therapy (HAART) for HIV-infected patients had a terrific impact and changed the story of the infection. In a consistent percentage of cases, HAART can efficiently suppress HIV production, by using the strategy of inhibiting different steps in the viral cycle and replication with the combination of drugs. According to WHO, >300 million people contract sexually transmitted infections every year. In developing countries, ~30% of women suffer from abnormal vaginal discharge due to reproductive tract infections (RTIs) caused by various pathogens (see chapter by Talwar). Talwar has developed a polyherbal formulation (Praneem) dispensed as a tablet, pessary or cream for topical vaginal use; it acts on a wide spectrum of genital pathogens. With the permission of the Drug Regulatory Agencies and Ethical Committees, phase II efficacy trials have been conducted in women with abnormal discharge due to pathogens. Once daily intake of Praneem over 7 days cured symptoms in 95% of women irrespective of the causative organisms.

Ravindranath and his colleagues turn to the immune system and cancer, relating the specific results from Genistein (4',5,7-trihydroxyisoflavone), a glycoside (genistin) in the plant family *Leguminosae*, which includes the soybean (*Glycine max*). A significant correlation between the serum/plasma level

of genistein and the incidence of gender-based cancers in Asian, European and American populations suggests that genistein may reduce the risk of tumor formation. Other evidence includes the mechanism of action of genistein in normal and cancer cells. Among other effects, Genistein can augment the efficacy of radiation for breast and prostate carcinomas. Because it increases melanin production and tyrosinase activity, genistein can protect melanocytes of the skin of Caucasians from UV-B radiation-induced melanoma. Genistein-induced antigenic alteration has the potential for improving active specific immunotherapy of melanoma and carcinomas.

TCM has so far been known to be useful for cancer patients as both an antitumor and an immuno-enhancing drug (see chapter by Wago and Deng). If some kinds of crude drugs of TCM possess such biological activities, they would be of great help in cancer treatment. This group tested a mixture of six kinds of crude drugs used for cancer patients in China named Ekki-Youketsu-Fusei-Zai (EYFZ), and its biological activities. They tested *in vitro* functional activation of macrophages and T lymphocytes, *in vivo* effects on natural killer (NK) cell activity and life prolongation in tumor-bearing mice, elucidating relationships between immuno-enhancement and antitumor influences.

A balanced state of wellness or homeostasis in patients translates into optimal adaptation to physical and psychological environments (see chapter by Roberts). In mammals, stressor exposure results in rapid, reflexive central nervous system (CNS) activation as part of the sympathetically mediated 'fight or flight' response. The inhibitory neurotransmitter γ -aminobutyric acid (GABA) is a key regulator of the integrated stress response, and low levels are implicated in the pathophysiology of diseases of adaptation: depression, bipolar disease and schizophrenia. Interactions between GABA and other neural and endocrine players give insights into homeostatic mechanisms essential for optimal wellness in a changing environment.

Tournaire presents alternative approaches to pain during labor and delivery. These alternatives can be divided into psychological, physical and chemical. Examples of the first group are: 'delivery without pain' or Lamaze method, sophrology, birth without violence of Leboyer, and haptonomy. In the second group, we find acupuncture reflex therapy, electrical anesthesia and delivery in water. Homeopathy encompasses the third use of plants. For centuries, pain associated with delivery has been denied or considered as God's creation that had to be accepted. Only recently has this pain, like others, been analyzed better and by more or less efficient means offered proposed was controlling it.

This section ends by giving examples of CAM in dentistry (see Komiyama), showing how a biomedical discipline is now combining technologies and ideas with those that are more traditional. It is well known that all dental treatments are almost all alternative, for example dentures where implants replace portions of missing teeth. As an approach, dentists have tried Chinese medicine on such intractable pain and achieved satisfactory results. They are now able to introduce a treatment

for patients with dry mouth, such as occurs with Sjögren's syndrome, that involves artificial saliva and galenicals.

Physical Intervention: Touch, Hydrotherapy and Sound

The section on physical intervention: touch, hydrotherapy and sound begins with acupuncture. Peter White has determined if acupuncture treatment is superior to a placebo intervention for chronic mechanical neck pain. Acupuncture was shown to be effective at reducing neck pain in the short and long term, but performed no better than the placebo treatment. The improvements in outcomes are therefore probably due to either the non-specific effects of treatment or regression to the mean, rather than the process of needling. With respect to disease, the onset of atopic dermatitis usually begins in infancy or childhood and some cases experience cure spontaneously before adolescence (see the chapter by Abo). Primarily, people in childhood show a high level of lymphocytes, gradually decreasing as adults. Apparently age-associated changes of the immune system are responsible for the spontaneous cure of atopic dermatitis. In other words, many cases of atopic dermatitis naturally subside due to an age-dependent decrease in the number of T cells. Gametocytes are activated further by many inflammatory cytokines, as well as by sympathetic nerve stimulation after the interaction with resident bacteria. Several factors must be considered, i.e. granulocyte function as well as functions of IgE, T cells and eosinophils, at least in severe cases of atopic dermatitis.

Along with treating illness, one aim of alternative medicine is to promote the QOL of healthy people. In Japan, centuries of tradition have shown that alternative therapies such as hot spring hydrotherapy, acupuncture and herbal medicine enhance the QOL of empirically healthy individuals (see the chapter by Yamaguchi). Accumulating evidence suggests immune system regulation. The scientific basis, however, has not yet been established. He proposes the numbers and functions of leukocyte subsets as indicators for evaluating alternative therapies as an indicator for the evaluation of alternative therapy that aims at the enhancement of the QOL of healthy people.

Music therapy (MT) is an established health profession using music and music activities or interventions and builds on the power of music, using music in a focused and concentrated way for healing and for change. It is a non-invasive medical treatment designed to prevent illness and disease, alleviate pain and stress, help people express feelings, promote physical rehabilitation, positively affect moods and emotional states, enhance memory recall, and provide unique opportunities for social interaction and emotional intimacy. Recounting the ancient texts, Scheve shows that data dating back to 6000 BC from Iraq identify music's role in magic, healing ceremonies and medicine. From a recent comeback, dating from 1914, there are now over 5000 music therapists employed throughout the USA in >50 different settings including hospitals, clinics, day care facilities, schools, community health centers, substance abuse facilities, nursing homes, hospices, rehabilitation centers, correctional facilities and private practices.

Bolstered by experimental evidence, music has been shown to modulate neuroendocrine molecules (see chapter by Wago and Kasahara). The hypothalamic-pituitary-adrenal (HPA) axis, melatonin, prolactin and biogenic amines (serotonin and catecholamines) are involved in altering functions of neuroendocrine substances in the brain in response to stressful inputs. Recent investigations on MT intervention for stress and behavioral modification is directed toward measurements of changes in stress-related neuroendocrine molecules such as cortisol. These studies suggest that the relaxing effects of music are critically involved in stimulation of neuroendocrine systems.

Dietary Intervention in Specific Diseases

Clearly dietary intervention is involved in the amelioration of disease (see chapter by Kobayashi). Atopic dermatitis is a disease whose main symptom is chronic recurrent eczematous lesions. Increased incidence and progression to intractable cases have become problems in recent years. For cases that do not resolve despite these efforts, concomitant Japanese traditional herb treatment has been used for >20 years. Since then, Japanese Traditional Medicine (JTM) has been used as a treatment concomitantly with modern Western medicine in all fields. A considerable time has passed since refractory atopic dermatitis increased gradually and became a social issue in Japan (see chapter by Ishii). Compared with the past, the disease appears to be more refractory already in children and most refractory in the adult type. Atopic dermatitis has been treated by Kampo (Japanese herbal medicine) therapies including dieting and achieved better results than by Western treatments alone, but there were difficulties in the demonstration of genuine effectiveness of Kampo therapies. Therefore, the effectiveness of Kampo therapies includes dieting in the most refractory cases, i.e. severe cases having persistent rash.

Turning now to India, ~70% of the Indian people live in rural areas and urban slums (see Kumar). Many of them are malnourished and suffer from various ailments. To address in a sustainable manner the nutritional and health needs of the poor (most of them vegetarian), the following 10 plants have proven particularly useful: *Spirulina* (cyanobacterium), neem (*Azadirachta indica*), turmeric (*Curcuma longa*), *Allium sativum*, *Aegle marmelos*, *Trigonella foeniculum graecum*, *Piper nigrum*, *Eugenia jambolina*, *Momordica charantia* and *Zingiber officinale*. Villagers in the vicinity of saline-alkaline wastelands can be trained to grow *Spirulina* themselves. Besides the above plants, regular daily consumption of 3–5 different-colored fruits/vegetables provides antioxidants and promotes all round good health.

Basic Science: Future Approaches to Novel Molecules for CAM

This is the most unique section in the book. This basic science approach offers a beginning and a long-range prediction of what might occur if we harness the countless number of substances from terrestrial and aquatic species as new

therapeutic aids. We should not forget that there is a substantial literature concerned with phytotherapy. However, derivatives from animals require more attention. Muller proposes the term evochemistry as an efficient natural strategy to develop bioactive compounds for medical use. As an example, sponges diverged first from a common metazoan ancestor, the Urmetazoa, ~800 million years ago. They are the richest animal phylum regarding bioactive compounds. It is suggested that the evochemical approach will result in the discovery of powerful bioactive compounds acting against specific human diseases. According to Cooper and his colleagues in Beijing, earthworms offer another rich source of molecules that have been characterized and shown to be strongly lytic against a variety of tumor cell targets grown *in vitro*. Also, apparently there is a need for molecules to be used in clinical situations, e.g. thrombosis. Lumbrokinase (LK) is a group of proteolytic enzymes, including plasminogen activator and plasmin, separated biochemically from earthworms. Few people know of the earthworm's long association with medicine and various remedies since 1340 AD. These old remedies may be resurrected in the current climate of CAM.

Roch poses the question: what can we learn from marine invertebrates to be used as complementary antibiotics? The main problem in infectious diseases is an alarming increase in resistance of microorganisms to classical antibiotics. We constantly need new molecules but most of them are derived from already used compounds. A better approach consists of developing molecules that possess totally different modes of action. Due to their life in hostile environments, marine invertebrates may have developed particular anti-infection systems and/or molecules. Shrimps and mollusks possess antimicrobial peptides routinely used by their innate immune system to prevent infections. Dissecting peptides produces various fragments with interesting *in vitro* antibacterial (*Staphylococcus*), antifungal (*Fusarium*), antiprotozoan (*Trypanosoma* and *Leishmania*) and antiviral (HIV) properties. Introducing modifications during chemical synthesis modulates activities, without inducing cytotoxicity. As patented molecules, their use in complementary medicine is under consideration.

As linkages, Kasahara and Cooper present the nervous, endocrine and immune systems as a target for CAM. Many aspects of CAM connect the three integrative systems: nervous, immune and endocrine. CAM, as we know, although controversial, is becoming a 'hot topic'. It is clearly recognized and acceptable in many academic and professional circles. We are reminded that homeostasis is a fundamental process essential for life under various stressors. Human health in a highly variable environment is dependent upon the proper balance of physiological processes. According to emerging views, homeostasis may be achieved by the coordinated activities of the three major integrative systems: the nervous, endocrine and immune

systems. The immune system has for a long time been considered as independent, but numerous recent studies have revealed it to be in a delicate state of balance with the neuro-endocrine system. There are a number of animal models that will allow us to dissect the gene control of modulation between neuro-endocrine and immune systems in relation to stress and diseases.

Education and Philosophy

Wallis, a philosopher, grapples with the important topic of placebo effects and how they may measure changes in socially learned behavior affected by a belief in the treatment. He delineates three different placebo debates: Freudian psychotherapy; pain perception; and depression. First, research suggests that a complex range of interactive causes are responsible for placebo effects that may constitute a spectrum from clinical chimeras to measurable neurobiological changes. Secondly, using this conception of placebo effects, objections do exist by mainstream scientists to research methods and results in several areas of CAM. Thirdly, controlling the range of possible sources of placebo effects is a challenge for mainstream science and CAM.

Finally, Loel introduces in his proposed new glycome, a medical paradigm. He rightly asserts that humans have the compassion, empathy and inventiveness to bring homeostasis to unfortunate individuals who lose their equilibrium. Throughout history, we have sought cures from the environment. Gods, herbs, laying-on of hands, bleeding, burning, sticking, starving and feeding have all been tried. Some are with us today in the form of acupuncture, chiropractic, homeopathy, and herbalist, spiritual and nutritional therapy. Computer technology has opened a new frontier—glycobiology. The new alternative therapy, glyconutrient support of cell-cell communication, is essential for a healthy immune response.

This book gives hope that scientists are turning their minds to this varied world of CAM that is growing in popularity day by day. All authors expressed the desire for an evidence base and the need to look with clear and intelligent eyes at the new trends that gather force around us. The energy of their curiosity and earnest questions was the single greatest catalyst for the birth of the new journal *eCAM* and I noticed that many of the names are now contributors to that journal. As a scientist in Japan searching for ways to create an evidence base for CAM modalities, I applaud their efforts and look forward to more brilliant words in the future.

This volume was edited by Edwin L. Cooper, University of California, Los Angeles and Nobuo Yamaguchi Kanazawa Medical University Uchinada, Ishikawa, Japan and published by Kluwer Academic/Plenum Publishers New York. It represents volume 546 of *Advances in Experimental Medicine and Biology*, contains 480 pages including an extensive index as well as about 100 figures and 35 tables.